

Efficacy of different interventions for the treatment of postherpetic neuralgia: a Bayesian network meta-analysis

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Abstract

Objective: We aimed to perform a network meta-analysis that combined both direct and indirect evidence to compare the relative efficacy of interventional therapies to treat patients with postherpetic neuralgia (PHN) and to determine the treatments' superiority and validity.

Method: A conventional paired meta-analysis was performed. This was followed by a network meta-analysis using the Bayesian framework.

Results: Botulinum toxin type A and pulsed radiofrequency (PRF) were the two most effective individual interventions. For combination therapy, PRF + nerve block (NB) was the best choice, followed by subcutaneous injection or local infiltration (SC) + NB + ozone (O₃). However, the combination of PRF + NB + SC showed reduced the efficacy compared with each treatment and was highly invasive for patients. After a long-term follow-up, PRF was shown to be the most effective therapy for treating patients with PHN.

Conclusions: Regular anti-neuropathic drug administration that was accompanied by interventional therapies at an early stage is the best choice to treat patients with PHN. Appropriate combinations of different interventions show improved pain relief. Clinicians should manage therapeutic regimens on the basis of the patients specific condition and existing measures and strive to achieve personalized treatment.

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Keywords

Interventional treatment, postherpetic neuralgia, radiofrequency, paravertebral block, dorsal root ganglion, botulinum toxin, stellate ganglion block

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Introduction

Postherpetic neuralgia (PHN) refers to pain that does not disappear after vesicular acute herpes zoster heals. PHN is conventionally defined as lasting more than 3 months after the onset of herpes zoster rash eruption or more than 1 month after the vesicles have healed.¹ PHN is the most common complication of shingles, with an incidence of 5% to 30% in patients with herpes zoster.² It is a persistent, debilitating, and chronic pain condition that is characterized by spontaneous pain, hyperalgesia, allodynia, and paresthesia in the dermatomal areas where shingles was present. Patients consider these troublesome syndromes to be intolerable, and they interfere the sleep and cause depression, thereby decreasing a patient's quality of life and leading to functional impairment and lost productivity.³ PHN causes an increase in the use of health care resources and an increased economic burden on society.^{2,4}

The priority in PHN treatment is to provide effective pain control and relieve sleep and emotional disorders, thereby improving the patient's quality of life. Currently, the primary therapy for PHN is early and sufficient administration of medication, including calcium channel regulators (such as pregabalin and gabapentin), antidepressants, lidocaine patches, tramadol, and opioids.⁵ However, medication alone does not always provide ideal efficacy, especially in patients with long-term PHN or with PHN in certain areas of the body. Moreover, some patients may experience

intolerable side effects of drugs such as nausea, dizziness, and drug addiction. These patients might benefit from interventional therapies. An interventional therapy refers to the technique that alleviates pain by directly targeting the lesion tissue and performing physical, chemical, or mechanical treatments, including nerve block (NB), selective nerve destruction, intrathecal drug administration, radiofrequency, nerve stimulation, ozone (O₃) therapy, and subcutaneous injection or local infiltration (SC).

Despite various interventions, there is no consensus on choosing an appropriate intervention or about each intervention's efficacy. Many clinical trials have been performed to compare the efficacy between two therapies, or between a therapy and drug administration, but most of them were observational studies or random controlled trials with a small sample size, which leads to unconvincing conclusions. Thus, some researchers have performed paired comparisons or a conventional meta-analysis between two methods and systematic reviews to assess the efficacy of these therapies.⁶⁻⁹ These studies provide direct comparisons and limited information, which are not as valuable as they could be, and it is necessary to compare and evaluate the clinical efficacy of these interventions on the basis of an overall viewpoint and provide a quantitative comparison and visualized conclusion.

In our study, we aimed to perform a network meta-analysis (NMA) among all available PHN interventional therapies, to

combine both direct and indirect evidence on PHN efficacy, to compare the relative efficacy of treatments for PHN, and to determine the PHN treatments' superiority and validity.

Methods

This NMA was designed and conducted in accordance with the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the PRISMA extension for NMAs.^{10,11}

Literature search strategy

Databases including PubMed, Embase, and the Cochrane Library were searched for studies about PHN treatments. The search was limited to literature that was published in English and before January 2020. To increase the comprehensiveness of our analysis, manual searches were performed using the reference lists from crucial studies and reviews. We used the following combined MeSH terms and their synonyms for the search: "Neuralgia, Postherpetic" and "Postherpetic Neuralgia". All searches were limited to human studies and clinical trial studies.

Inclusion and exclusion criteria

To be included in our NMA, studies fulfilled the inclusion criteria that were interpreted under the PICOS framework (P, patients; I, interventions; C, controls; O, outcomes; S, studies) as follows: 1) P: Patients with PHN in body areas that were innervated by spinal nerves; 2) I: Interventional treatments were applied to the treatment groups, as follows: NB (including epidural block, spinal NB, dorsal root ganglion block, intercostal NB, paravertebral block), SC (including subcutaneous injection of normal saline, local anesthetics, corticosteroids, MeB12

as well as local infiltration), stellate ganglion block (SGB), subcutaneous botulinum toxin type A (BTX-A) injection, and pulsed radiofrequency (PRF) with or without administration of drug therapy; 3) C: Another interventional therapy or sham procedure or blank control was used for the control groups; 4) O: At least one quantitative pain evaluation can be extracted in all enrolled studies; and 5) S: Randomized controlled clinical trials.

The exclusion criteria for the studies were as follows: 1) Studies conducted in patients who had other neuropathic pain; 2) Studies focusing on destructive methods; or 3) Studies without a clear description of the study design, specific interventions, or necessary information about the participants.

Studies identified by our search were independently selected by two authors, and disagreements were resolved by consensus or consulting with another author. Titles and abstracts were reviewed first to determine whether studies were related to the theme. Then, full articles were judged on the basis of the inclusion and exclusion criteria. If a study satisfied the inclusion criteria, it was included for data extraction and used in the detailed analysis.

Data extraction and quality assessment

Two authors independently performed the data extraction and quality assessment for the selected studies; all disagreements were resolved by consensus.

Data were extracted on the basis of a prespecified table including the following contents: 1) demographic data (total number of participants, age, sex, necessary information about PHN); 2) treatment protocols (methods, route, drug category, and dosage); 3) outcomes; and 4) any complications.

The quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias, which includes the following seven aspects: random

sequence generation; allocation concealment; blinding of patients and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other sources of bias (adequate description of sample size calculation and detailed disclosure of funding sources). RevMan5.3 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) was used to judge bias, which was expressed as “high risk,” “low risk,” or “unclear risk.”

Statistical analysis

Pain intensity was the only outcome that was analyzed in this study, and it was evaluated using different pain scales such as the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS), which were described in the included studies. Thus, the mean difference (MD) was used to compare the relative differences between different groups. Because all of the included studies were RCTs, the baseline pain score was comparable between different groups within a trial, so we mainly compared the pain scores using the endpoints.

For the direct comparison, the results were described as the MD and 95% confidence intervals (CIs), and for the indirect comparison and mixed-treatment effect, MD and 95% credible intervals (CrIs) were used. Because a lower pain scale means a better effect, a negative MD showed if a particular therapy was more effective than another therapy.

We initially performed a conventional paired meta-analysis to compare the relative efficacy between two treatments. The I^2 test was used to evaluate heterogeneity among the included studies.^{12,13} The heterogeneity was considered to be low, moderate, or high for I^2 values <25%, 25% to 50%, or >50%, respectively.¹⁴ Because of the small number of studies that can be used for direct comparisons, the DerSimonian–Laird (DL)

random effects (RE) model was used for the paired meta-analysis.

Then, we performed NMA among all treatments using the Bayesian framework. The node-splitting method and the inconsistency factor were used to analyze the inconsistency between direct and indirect comparisons. The publication bias was assessed using funnel plots. Network plots, funnel plots, and cumulative probability plots were obtained using Stata 14.0 (StataCorp LLC, College Station, TX, USA), and NMA and the paired meta-analysis were performed using ADDIS (Department of Epidemiology, University Medical Center, Groningen, The Netherlands). $P < 0.05$ was considered to be statistically significant.

Results

Study selection

As shown in Figure 1, 828 studies were identified from the above-mentioned databases, and 25 studies were obtained via a manual search. After removing duplicates, 709 studies remained in the primary selection, and 550 of them were excluded based on their title and abstracts, leaving 159 studies for full-text evaluation on the basis of the inclusion and exclusion criteria. After reading the full text, 147 studies were excluded with explanations, and 12 studies were included in our NMA.

Study characteristics

Table 1 describes the summary of the 12 included studies that were published between 2010 and 2017.^{15–26} There were 702 participants with an age range from 57.06 to 73.53 years. Among these included studies, two focused on the efficiency of subcutaneous BTX-A,^{21,26} three focused on NB,^{15–17} five studies focused on PRF therapy,^{15,16,19–21} one study focused on

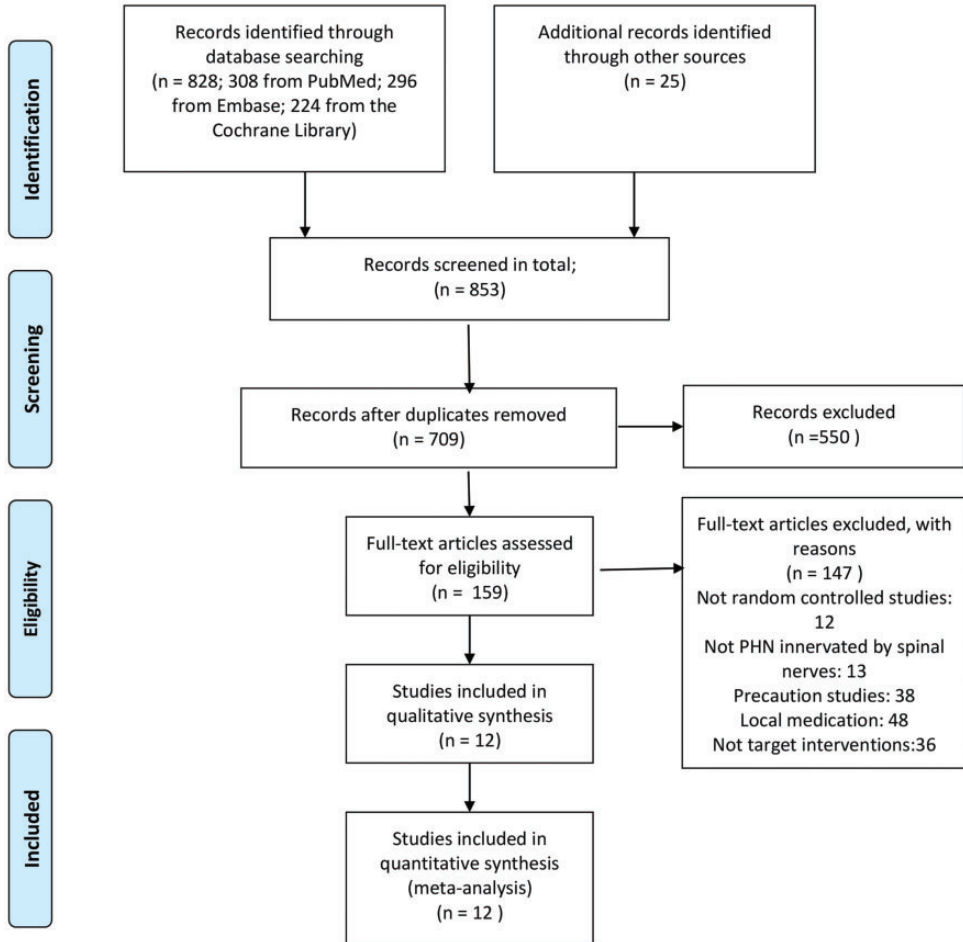


Figure 1. Flowchart for study selection.

PRF + NB,¹⁷ one study focused on PRF + NB + SC,¹⁹ three studies focused on SC,^{23,24,26} one study focused on SC + NB,²⁴ one study focused on SC + NB + O3 injection,²⁴ and one study focused on SGB.²⁵ The detailed parameters, methods, and drug dosages are listed in Table 1. For oral medication, among nine studies,^{16–24} all patients regularly took oral calcium channel regulators (first-line drugs for PHN treatment); however, in one study,²⁵ only some patients took calcium channel regulators, while in two studies,^{26,27} no patients took these medications.

Quality of the included studies

Studies included in our NMA were assessed using the Cochrane Collaboration's tool for assessing the risk of bias (Figure 2). All 12 of the included studies reported all of the results, and most studies^{16–22,24–27} described how the random sequence was generated and showed all of the outcome data. Half of the included studies^{19–22,26,27} showed their allocation concealment method and outcome concealment strategy, while two studies^{19,23} did not perform blinding for their participants and personnel. The publication bias for the included studies is

Table 1. Characteristics of the included studies.

Audior, Year	Study Design	Mean Age (years)	Female (%)	Duration of PHN	Pain Intensity	Body Area	Follow-up	Pain Scale
Ashok, 2016 ²² Dan, 2018 ¹⁷	Double-blind RCT RCT	60.17 67	43.30 -	>3 months >1 month	VAS \geq 30 mm -	T3-T11 Cervical or thoracolumbar	8 weeks 12 hours	VAS VAS
Dong, 2017 ¹⁹	Single-blind RCT	69.98	69.70	>3 months	-	Abdominal and thoracic back	48 hours	VAS
Gang, 2013 ²³	RCT	66.93	52.04	1 month-3 months	NRS \geq 4	-	4 weeks	NRS
Guo, 2013 ²⁴ Ji, 2012 ²⁵ Lizu, 2010 ²⁶	RCT RCT Double-blind RCT	57.06 63.5 67.33	47.06 40 53.33	>1 month - >3 months	- - VAS \geq 5	Chest and back Orofacial, cervical and upper extremity, lumbar and lower extremity	4 weeks 8 weeks 3 months	VAS VAS VAS
Ma, 2013 ²⁰ Mohamed, 2018 ²¹ Wang, 2012 ¹⁸ Xia, 2018 ¹⁶	Double-blind RCT Double-blind RCT RCT RCT	72.16 58.74 67.2 66.47	50.00 44.19 44.23 50.0	\geq 6 months >6 months >3 months 4 months-3 years	VAS >30 mm VAS >30 mm VAS >6 -	T2-T11 T2-T11 Thoracic and back Abdominal and thoracic area	6 months 1 year 12 weeks 12 weeks	VAS VAS VAS NRS
Zoe, 2013 ²⁷	Double-blind RCT	75.35	40%	\geq 3 months	VAS \geq 7	Thoracic, sciatic, brachial plexus	20 weeks	VAS
Audior, Year	Evaluation time point	Basic Drugs	N	Groups, n	Dose	Route		Adverse events related to interventional treatment
Ashok, 2016 ²²	Basic, 1 week, 2 weeks, 4 weeks, 8 weeks	Pregabalin; tramadol as rescue	60	PRF, 30; sham, 30	42°, 180 s; -	Intercostal	2 local site reactions; 2 local site reactions	
Dan, 2018 ¹⁷	Basic, 12 hours after treatment	Gabapentin; tramadol	60	Conventional puncture, 15; NB, 15; PRF, 15; PRF+NB, 15	-; mecobalamin 1 mg/mL, extract from rabbit skin inflamed by vaccinia virus for injection 6 mL, 1% ropivacaine 2 mL; 0.9% normal saline 11 mL; 42°, 100 s \times 3; PRF followed by NB	Paravertebral	None	

(continued)

Table 1. Continued.

Dong, 2017 ¹⁹	Basic, 48 hours after treatment	Pregabalin; diclofenac; cobamamide	32	Control, 18; PRF+NB+SC, 15	-; 42°, 120 s × 2 + 5 mL (lidocaine + ropivacaine + betamethasone + cobamamide + NS)	DRG+SC	-
Gang, 2013 ²³	Basic, 1 week, 2 weeks, 4 weeks	Gabapentin or pregabalin	98	MeB12 injection, 33; oral MeB12, 33; SC lidocaine injection, 32	1 mg MeB12; 0.5 mg MeB12 t.i.d.; 1% lidocaine	SC; oral; SC	-
Guo, 2013 ²⁴	Basic, 4 weeks	Gabapentin, ibuprofen codeine, VitrB12	80	SC + oral MeB12, 20; paravertebral block + SC, 20; paravertebral block + O3 injection + SC, 21;	Ropivacaine 10 mg + betamethasone 1 mg + NS 20 mL; ropivacaine 10 mg + betamethasone 1 mg + NS 20 mL; Ropivacaine 10 mg + betamethasone 1 mg + NS 20 mL; ropivacaine 10 mg + betamethasone 1 mg + NS 20 mL + O3 35 µg/mL	SC; SC; paravertebral paravertebral	-
Ji, 2012 ²⁵	Basic, 1 week, 2 weeks, 3 weeks, 4 weeks, 8 weeks	Pregabalin, celecoxib as rescue	120	SGB, 40; Pregabalin, 40; SGB + pregabalin, 40	0.5% lidocaine 10 mL; -; 0.5% lidocaine 10 mL	SGB	1 hoarseness, 1 hematoma; -; 2 hoarseness, 1 hematoma
Lizu, 2010 ²⁶	Basic, 1 day, 7 days, 3 months	Opioid as rescue	60	BTX-A, 20; Lidocaine, 20; placebo, 20	5 IU/mL (100 IU in total) BTX-A; 0.5% lidocaine; NS	SC	None
Ma, 2013 ²⁰	Basic, 3 days, 1 weeks, 2 weeks, 1 month, 2 months, 3 months, 6 months	Gabapentin; antidepressants; tramadol	92	PRF, 46; sham, 46	42°, 120 s × 2; -	Intercostal	1 bradycardia; 1 needle injury
Mohamed, 2018 ²¹	Basic, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks, 12 weeks, 14 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks, 6 months, 9 months, 12 months	Pregabalin; acetaminophen as rescue	43	PRF, 21; sham, 22	42°, 120 s × 2; -	Intercostal	None

(continued)

Table 1. Continued.

Wang, 2012 ¹⁸	Basic, 1 weeks, 2 weeks, 3 weeks, 4 weeks, 8 weeks, 12 weeks	Pregabalin	52	Thoracic paravertebral nerve block, 27; only drug, 25	0.3% lidocaine 10 mL + triamcinolone 10 mg -	Paravertebral	None		
Xia, 2018 ¹⁶	Basic, 2 weeks, 4 weeks, 12 weeks	Gabapentin	60	Acupuncture trigger point, 20; continuous epidural nerve block, 20; selective DRG PRF, 20	-; 2 mL/hour (ropivacaine 225 mg + betamethasone + cobamide + NS); 42° 10 minutes with an interval of 15 s	-; epidural; DRG	-		
Zoe, 2013 ²⁷	Basic, every day in the first 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks	Paracetamol	30	BTX-A, 15; NS, 15	100 IU + 4 mL NS; 4 mL NS only	SC; SC	None		

RCT, random controlled trial; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A; DRG, dorsal root ganglion; NS, normal saline; T, thoracic nerve; VAS, visual analog scale; NRS, numerical rating scale; IM, intramuscular; t.i.d., three times daily; -, data not available from the original article.

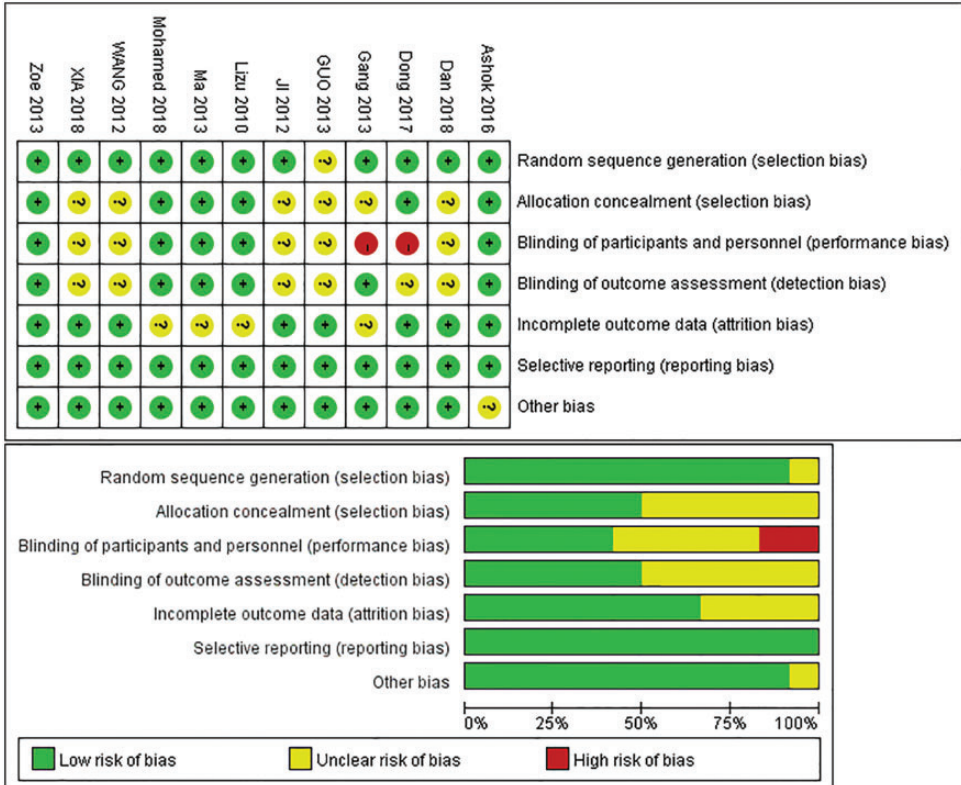


Figure 2. Bias assessment graph.

shown in Figure 3. The data points were grouped in the middle and upper parts of the funnel plot, and most of the data points were contained within the 95% CI lines, indicating that the publication bias was relatively low.

Pairwise comparison

As shown in Figure 4, we chose the three most common time points (1 week, 1 month, and 3 months after treatment) to conduct 22 paired meta-analyses between each group of two interventions, and the results are presented as the MD and 95% CI. The analyzed outcome was pain intensity, and a negative MD meant that the

former intervention was better than the later intervention.

After 1 week of treatment, there were 12 pairwise comparisons, and the results are shown in Figure 4A. In contrast to oral medications, five treatment classes showed a significant effect on pain relief, including NB, PRF, PRF + NB, PRF + NB + SC, and SC. Additionally, SGB was not superior to oral medications. Compared with SC, subcutaneous BTX-A injection and SC + NB + O3, but not SC + NB, showed significant efficacy. Compared with NB, neither PRF nor PRF + NB was more effective, while PRF + NB showed the best effectiveness.

After 1 month of treatment, six paired comparisons were performed, and the

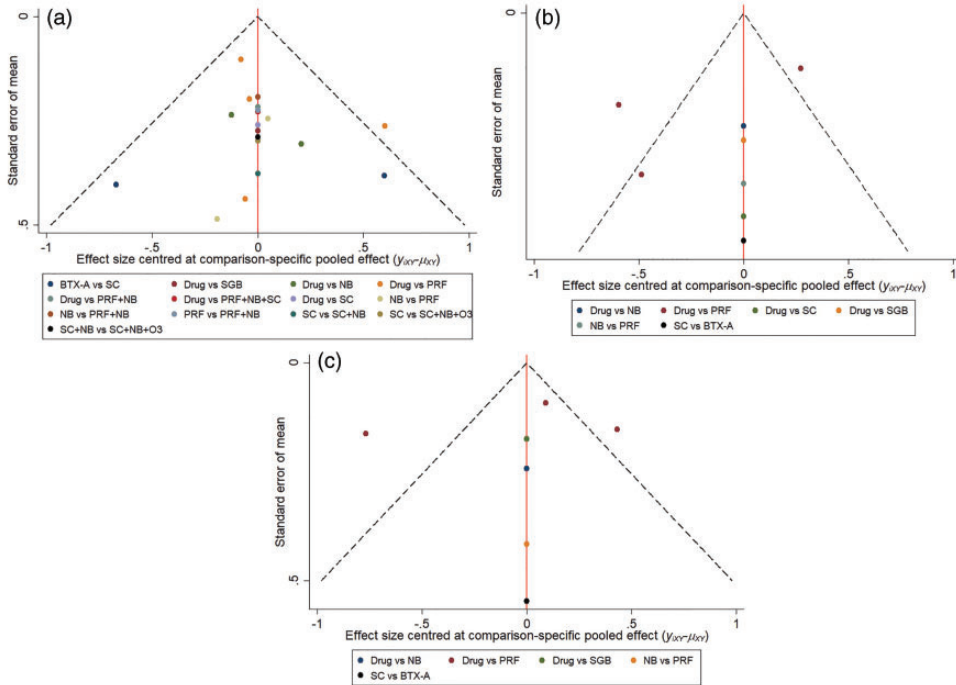


Figure 3. Comparison-adjusted funnel plot. (a) Comparison-adjusted funnel plot for 1 week after treatment, (b) Comparison-adjusted funnel plot for 1 month after treatment, (c) Comparison-adjusted funnel plot for 3 months after treatment. Drug, oral drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A.

results are shown in Figure 4B. The efficacy of PRF, SC, and SGB was better than that of oral medications, and NB showed no significant difference from oral medications. PRF was also more effective for pain relief than NB.

Three months after treatment, paired comparisons showed that PRF and SGB, but not NB, were more effective than oral medications. Subcutaneous BTX-A injection was still more effective than SC (Figure 4C).

Network meta-analysis

Figure 5 shows network plots of 1 week, 1 month, and 3 months after treatments. The NMA outcomes showing the relative effects

and 95% CrIs are presented in Table 2. A negative number indicates better efficacy, a 95% CrI including zero means that there is no significant difference between two interventions. The NMA was accomplished using Bayesian analysis methods, which are based on the Markov chain–Monte Carlo method. NMA results were similar to the direct paired comparisons above, but they offered more information, as described below.

After 1 week of treatment, as shown in Figure 5A and Table 2A, comparisons were made among six independent interventions and four combined therapies. Among all of these therapies, subcutaneous BTX-A injection was more effective than the other treatments except for PRF + NB and

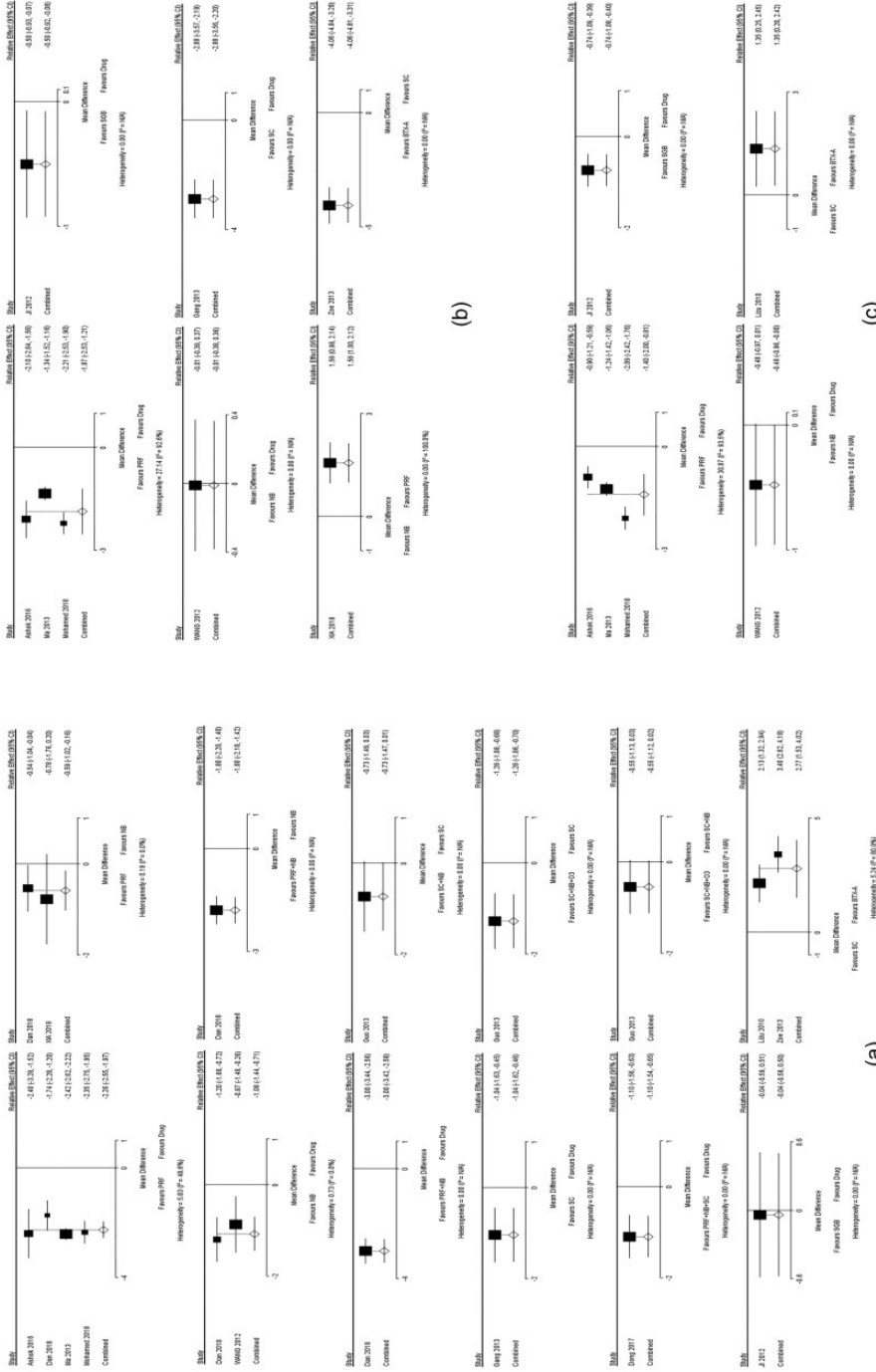


Figure 4. Forest plot for the direct comparison of the pain score 1 week after treatment, (a) Forest plot for the direct comparison of the pain score 1 month after treatment, (c) Forest plot for the direct comparison of the pain score 3 months after treatment. A negative MD means that the efficacy of the former therapy is better than that of the latter therapy

CI, confidence interval; Drug, oral drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A; MD, mean difference.

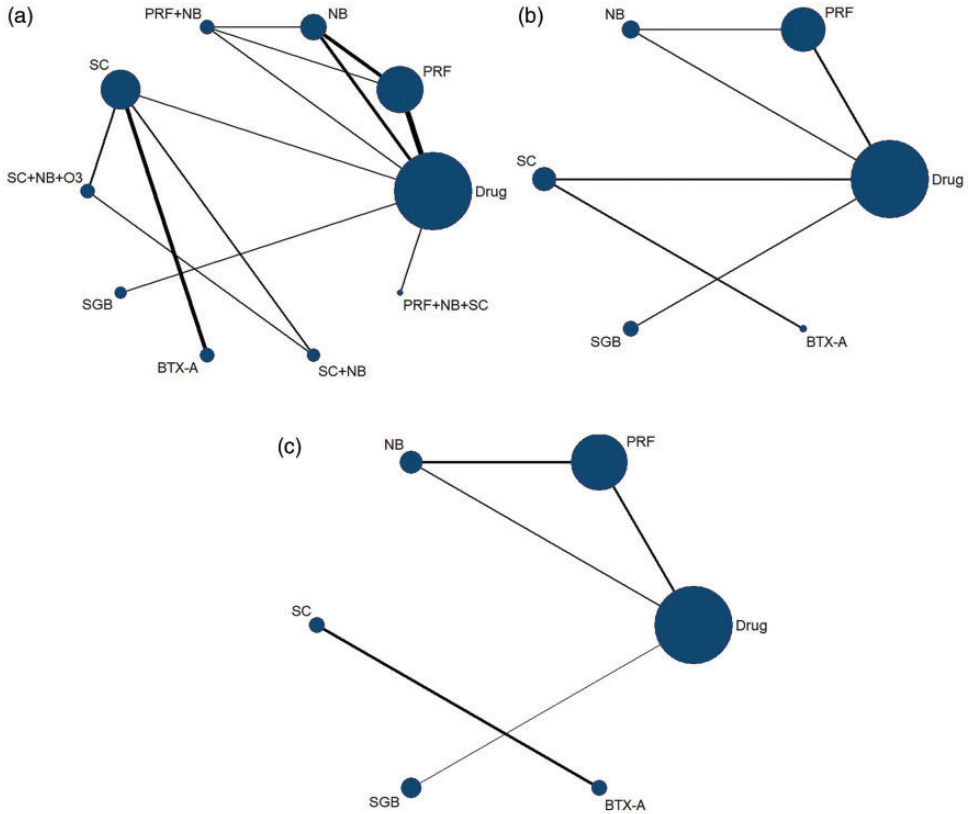


Figure 5. Network evidence plot. (a) Network evidence plot 1 week after treatment, (b) Network evidence plot 1 month after treatment, (c) Network evidence plot 3 months after treatment. The size of the blue circles describes the total number of participants in each treatment class, and the thickness of the black lines between two circles describes the total number of studies that compared the two treatment classes Drug, oral drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A.

SC + NB + O3. Oral medication alone was less effective than other treatments except for SC and SGB. For NB, SC, PRF, and their combinations, PRF + NB exhibited a significant improvement in pain relief compared with the other treatments, while PRF + NB + SC was not significantly effective compared with the other treatments, and NB was less effective than PRF.

After 1 month of treatment, outcomes between the comparison of six therapies are shown in Figure 5B and Table 3B. BTX-A was more effective than the other treatments. Thus, PRF was significantly

better than oral medications and NB for alleviating pain.

After 3 months of treatment, Figure 5C and Table 2C show that PRF was significantly better than oral medications. For all other comparisons, the 95% CrI included zero.

Consistency assessment

We performed this NMA based on the consistency model. To evaluate its validity, we used the following two methods: node-splitting method and inconsistency factors.^{27,28} The results are shown in Table 3.

Table 2A. The league table of NMA results for pain score 1 week after treatment.

BTX-A	3.81 (2.35, 5.28)	2.55 (0.98, 4.21)	1.61 (0.05, 3.22)	0.64 (-1.08, 2.46)	2.73 (0.85, 4.52)	2.77 (1.88, 3.66)	2.03 (0.48, 3.60)	1.49 (-0.05, 2.94)	3.78 (1.86, 5.67)
Drug									
-3.81 (-5.28, -2.35)	-1.27 (-1.93, -0.53)	-2.21 (-2.73, -1.63)	-3.17 (-4.13, -2.17)	-1.10 (-2.24, -0.02)	-1.05 (-2.22, 0.12)	-1.77 (-3.58, -0.07)	-1.77 (-3.58, -0.07)	-2.31 (-4.04, -0.64)	-0.04 (-1.19, 1.15)
-2.55 (-4.21, -0.98)	NB	-0.94 (-1.66, -0.24)	-1.90 (-2.94, -0.90)	0.16 (-1.20, 1.45)	0.24 (-1.17, 1.53)	-0.49 (-2.42, 1.26)	-0.49 (-2.42, 1.26)	-1.04 (-2.96, 0.70)	1.23 (-0.18, 2.59)
-1.61 (-3.22, -0.05)	0.94 (0.24, 1.66)	PRF	-0.96 (-1.97, -0.01)	1.12 (-0.23, 2.30)	1.17 (-0.19, 2.43)	0.44 (-1.48, 2.17)	0.44 (-1.48, 2.17)	-0.10 (-1.94, 1.62)	2.16 (0.82, 3.42)
-0.64 (-2.46, 1.08)	1.90 (0.90, 2.94)	0.96 (0.01, 1.97)	PRF+NB	2.08 (0.50, 3.49)	2.13 (0.55, 3.61)	1.41 (-0.71, 3.34)	1.41 (-0.71, 3.34)	0.85 (-1.21, 2.79)	3.13 (1.57, 4.69)
-2.73 (-4.52, -0.85)	-0.16 (-1.45, 1.20)	-1.12 (-2.30, 0.23)	-2.08 (-3.49, -0.50)	PRF+NB+SC	0.05 (-1.53, 1.72)	-0.68 (-2.80, 1.40)	-0.68 (-2.80, 1.40)	-1.23 (-3.31, 0.77)	1.07 (-0.52, 2.74)
-2.77 (-3.66, -1.88)	-0.24 (-1.53, 1.17)	-1.17 (-2.43, 0.19)	-2.13 (-3.61, -0.55)	SC	0.72 (-0.51, 2.06)	SC+NB	SC+NB	-1.27 (-2.49, -0.09)	1.00 (-0.63, 2.65)
-2.03 (-3.60, -0.48)	0.49 (-1.26, 2.42)	-0.44 (-2.17, 1.48)	-1.41 (-3.34, 0.71)	0.68 (-1.40, 2.80)	1.27 (0.09, 2.49)	0.56 (-0.66, 1.73)	0.56 (-0.66, 1.73)	-0.56 (-1.73, 0.66)	1.72 (-0.36, 3.91)
-1.49 (-2.94, 0.05)	1.04 (-0.70, 2.96)	0.10 (-1.62, 1.94)	-0.85 (-2.79, 1.21)	1.23 (-0.77, 3.31)	1.27 (0.09, 2.49)	SC+NB+O3	SC+NB+O3	2.27 (0.28, 4.37)	5GB
-3.78 (-5.67, -1.86)	-1.23 (-2.59, 0.18)	-2.16 (-3.42, -0.82)	-3.13 (-4.69, -1.57)	-1.07 (-2.74, 0.52)	-1.00 (-2.65, 0.63)	-1.72 (-3.91, 0.36)	-1.72 (-3.91, 0.36)	-2.27	5GB
								$\chi^2(-4.37, -0.28)$	

Table 2B. The league table of NMA results for pain score 1 month after treatment.

BTX-A	6.92 (3.79, 9.96)	6.81 (3.35, 10.18)	5.10 (1.82, 8.35)	4.05 (1.96, 6.14)	6.43 (2.73, 10.06)
-6.92 (-9.96, -3.79)	Drug				
-6.81 (-10.18, -3.35)	0.12 (-1.51, 1.74)	-0.12 (-1.74, 1.51)	-1.83 (-3.00, -0.70)	-2.88 (-5.02, -0.73)	-0.51 (-2.58, 1.57)
-5.10 (-8.35, -1.82)	1.83 (0.70, 3.00)	NB	-1.70 (-3.33, -0.12)	-2.77 (-5.50, 0.03)	-0.37 (-3.05, 2.31)
-4.05 (-6.14, -1.96)	2.88 (0.73, 5.02)	1.70 (0.12, 3.33)	PRF	-1.06 (-3.46, 1.42)	1.32 (-1.15, 3.73)
-6.43 (-10.06, -2.73)	0.51 (-1.57, 2.58)	2.77 (-0.03, 5.50)	1.06 (-1.42, 3.46)	SC	2.38 (-0.60, 5.36)
		0.37 (-2.31, 3.05)	-1.32 (-3.73, 1.15)	-2.38 (-5.36, 0.60)	5GB

Table 2C. League table of NMA results for pain score 3 months after treatment.

Drug	-0.17 (-1.72, 1.42)	-1.51 (-2.62, -0.42)	-0.74 (-2.80, 1.27)
0.17 (-1.42, 1.72)	NB	-1.34 (-2.98, 0.26)	-0.58 (-3.09, 2.08)
<u>1.51 (0.42, 2.62)</u>	1.34 (-0.26, 2.98)	PRF	0.76 (-1.56, 3.08)
0.74 (-1.27, 2.80)	0.58 (-2.08, 3.09)	-0.76 (-3.08, 1.56)	SGB

Therapies are reported in alphabetical order. Data are described as the MD and 95% CrI. A 95% CrI that includes zero means that there is no significant difference between two therapies. A negative MD favors the column-defining therapy. Significant results are in bold and underscored.

Drug, drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A; NMA, network meta-analysis; MD, mean difference; CrI, credible interval.

Table 3A. Results of node-split analysis.

Time	Name	Direct Effect	Indirect Effect	Overall	P-Value
1 week	Drug, NB	-1.12 (-2.00, -0.14)	-1.43 (-3.13, 0.20)	-1.27 (-1.93, -0.53)	N.S.
	Drug, PRF	-2.24 (-2.93, -1.56)	-1.86 (-3.68, -0.02)	-2.21 (-2.73, -1.63)	N.S.
	NB, PRF	-0.63 (-1.36, 0.10)	-1.33 (-2.18, -0.47)	-0.94 (-1.66, -0.24)	N.S.
1 month	Drug, NB	-0.01 (-3.13, 3.15)	-0.31 (-3.81, 3.40)	-0.12 (-1.74, 1.51)	N.S.
	Drug, PRF	-1.85 (-3.59, -0.10)	-1.58 (-5.88, 2.52)	-1.83 (-3.00, -0.70)	N.S.
	NB, PRF	-1.59 (-4.80, 1.70)	-1.86 (-5.83, 1.85)	-1.70 (-3.33, -0.12)	N.S.
2 months	Drug, NB	-0.50 (-2.74, 1.84)	0.37 (-2.28, 3.08)	-0.17 (-1.72, 1.42)	N.S.
	Drug, PRF	-1.41 (-2.75, -0.10)	-2.24 (-5.62, 1.01)	-1.51 (-2.62, -0.42)	N.S.
	NB, PRF	-1.74 (-4.14, 0.60)	-0.94 (-3.62, 1.72)	-1.34 (-2.98, 0.26)	N.S.

Table 3B. Inconsistency factor.

Time Point	Cycle	Inconsistency Factor, median (95%CrI)
1 week	Drug, NB, PRF	0.06 (-3.03, 2.20)
1 month	Drug, NB, PRF	0.10 (-2.07, 2.31)
2 months	Drug, NB, PRF	-0.17 (-2.06, 1.39)

Data were described as MD and 95% CI or 95% CrI. $P \leq 0.05$ indicates a statistically significant difference between direct and indirect effects. An inconsistency factor close to zero means that there was no significant inconsistency between the direct and indirect therapy.

Drug; drug therapy; PRF, pulsed radiofrequency; NB, nerve block; MD, mean difference; CI, confidence interval; CrI, credible interval; N.S., not significant.

The node-splitting analysis assessed whether indirect and direct evidence were in agreement on a split node.²⁹ Table 3A shows the node-splitting analysis results at different time points after treatment, including direct, indirect, and combined evidence. The P-value was also shown to

indicate whether there was significant inconsistency. $P \leq 0.05$ was considered to be statistically significant. Table 3A suggests that no significant inconsistency was present in the NMA. Moreover, it is meaningful to assess the consistency using the node-splitting analysis only when there is

concurrent direct and indirect evidence. Thus, the consistency could not be assessed for comparisons using only an indirect comparison.

If closed loops are present in the evidence structure, the inconsistency factor can be used to detect the inconsistency. The closer the inconsistency factor is to zero, the smaller the amount of inconsistency that is present.²⁸ The results are summarized in Table 3B, which indicates that there is no significant inconsistency. This is in agreement with the results of the node-splitting analysis.

Ranking of treatment classes

The Bayesian approach allows estimation of the probability, provides the different previous therapies, and the data so that the best treatment can be identified,

followed by the second-best treatment and so on. The results are shown in Figure 6 and Figure 7. Figure 6 shows the rank probabilities for each treatment. The sum of the rank probabilities is 1, whether it is within a rank over treatments or within a treatment over ranks. Rank 10 indicates the best treatment for pain reduction. Figure 7 shows the cumulative probability of different therapies, and larger areas under the curve mean a smaller rank and worse pain relief efficacy. After 1 week of treatments, subcutaneous BTX-A ranked the best and PRF+NB ranked the second best, followed by SC+NB+O3 and PRF; SC+NB, NB, PRF+NB+SC, and SC; and the last two were SGB and oral medication. After 1 month of treatment, the ranking sequence from the most to least effective was as follows: BTX-A, SC, PRF, SGB, NB, and oral medication.

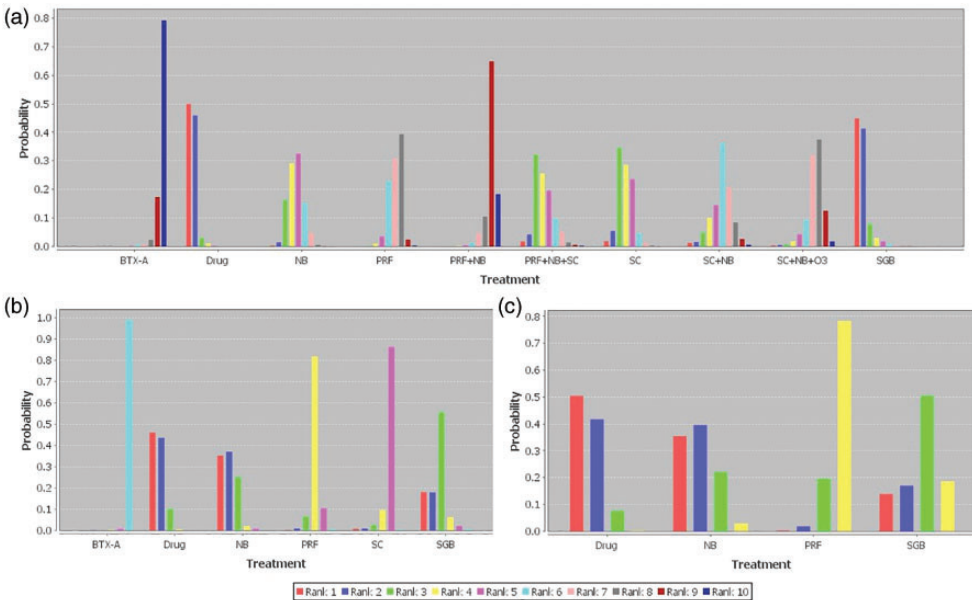


Figure 6. Rank probability plot. (a) Rank probability plot for pain score 1 week after treatment, (b) Rank probability plot for pain score 1 month after treatment, (c) Rank probability plot for pain score 3 months after treatment. Rank 1 is the worst and rank 10 is the best rank. Drug, oral drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A.

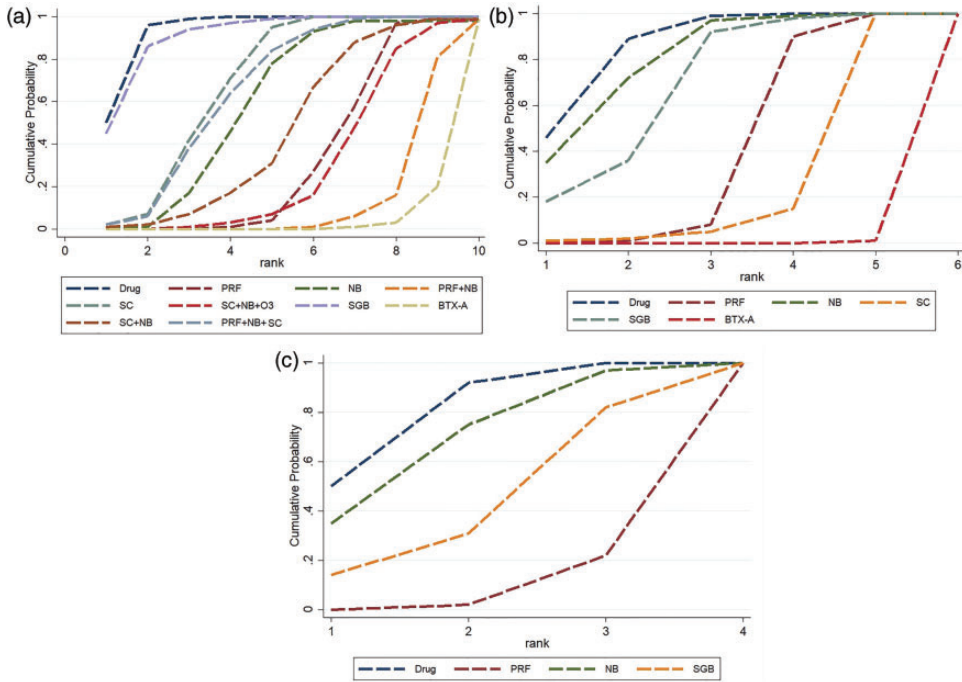


Figure 7. Cumulative probability plot. (a) Cumulative probability plot for the pain score 1 week after treatment, (b) Cumulative probability plot for the pain score 1 month after treatment, (c) Cumulative probability plot for pain score 3 months after treatment. The larger the area under each curve, the less effective the treatment is for pain reduction. Drug, oral drug therapy; PRF, pulsed radiofrequency; NB, nerve block; SC, subcutaneous injection or local infiltration; O3, ozone injection; SGB, stellate ganglion block; BTX-A, botulinum toxin type A.

After 3 months of treatment, the sequence was as follows: PRF, SGB, NB, and oral medication.

Discussion

Currently, there are various interventions to treat patients with PHN. For a pain physician, choosing a suitable treatment for a particular patient is vital. Although many studies have been performed to explore each measure’s roles, there was still a lack of overall and quantitative studies among all treatments. To evaluate the efficiency of different interventions, we performed this NMA (including direct and indirect comparisons and mixed treatment comparisons). Twelve RCT studies, including 702

patients and ten treatments, were analyzed. Each included study had compared one, two, or three types of interventions at different time points after therapy. To simplify our NMA, we chose the three most common time points (1 week, 1 month, and 3 months) to analyze.

Through direct pairwise comparison at 1 week, interventions other than SGB all had a better therapeutic effect than oral drug therapy, indicating the requirement for early intervention in addition to the correct oral medication. For PRF and NB, which are the two most commonly used therapies, the efficacy of PRF was better than that of NB, while the combination of these therapies was better than using them alone. For SC, SC + NB had no significant advantages

over SC, but if O3 was injected with NB+SC, the efficacy was better than either of these treatments alone. Additionally, subcutaneous injection of BTX-A was better than subcutaneous injection of saline or lidocaine. After 1 to 3 months of treatment, almost all of the interventions had better efficacy than that of oral drug therapy.

The results of this NMA were similar to those of the direct comparison, but the NMA provided more information for treatments without direct comparisons. After 1 week of treatment, PRF+NB+SC (ranked fourth) was not significantly better than NB (ranked fifth), PRF (ranked seventh), or NB+PRF (ranked ninth), but it was better than SC (ranked third). Additionally, subcutaneous injection of BTX-A (ranked tenth) was significantly more effective than other therapies, except PRF+NB and SC+NB+O3. Furthermore, combination therapies, including PRF+NB, SC+NB, and SC+NB+O3, showed comparable efficacy and were superior to each therapy alone except for BTX-A. After 1 month of treatment, BTX-A was still ranked the best, while SC (ranked fifth) was better than PRF (ranked fourth), but the difference was not significant. SGB (ranked third) was better than NB (ranked as the second) and oral medication (ranked first). After 3 months of treatment, the order of priority was PRF, SGB, NB, and oral medication.

PRF is a commonly used neuromodulation therapy in pain management, and it is characterized as highly selective and minimally invasive.³⁰ Compared with continuous radiofrequency therapy, PRF produces a rapidly changing electric field and lower temperature; thus, it is safer and easier to use, and it causes fewer complications such as neural damage and post-operative soreness. PRF can block pain transmission by interrupting signals in unmyelinated C fibers and myelinated A-

delta fibers without influencing myelinated A-alpha and A-beta fibers.³¹ Moreover, PRF appears to change c-fos mRNA expression in the dorsal horn of spinal cord.³² In our NMA, PRF was highly effective for pain reduction in PHN patients at all time points compared among all the analyzed interventions. It can alleviate pain for a long time and promote curing patients with PHN. Overall, considering its strong safety profile, minimal invasiveness, fewer adverse effects, and nondestructive nature, PRF is easily accepted by both patients and doctors, and it is an appropriate intervention for PHN.

NB is a minimally invasive therapy, which means injecting mainly local anesthetics or drugs including local anesthetics (sometimes steroids may be added) into the nerve root, trunk, ganglion, or epidural space. In our analysis, NB includes epidural block, dorsal root ganglion block, intercostal NB, and paravertebral block. NB can temporally block nerve transduction without damaging the nerves. Our NMA showed that NB was valid at all the analyzed time points, but at 1 month and 3 months, the efficacy rank of NB decreased. This phenomenon indicates that the effect of NB is transient, persisting for a short period. However, NB is beneficial to for the PHN patient's prognosis over the long term.

NB is also synergistic with PRF and SC, and their combination was better than each treatment alone. Thus, NB is safe, convenient, and easy to perform, it is good for temporary anesthesia, and application of NB in the early stage of PHN can promote pain relief for a long time. If permitted, continuous blockade or the combination of NB with PRF or SC are good choices.

SC, in our study, includes subcutaneous injection of lidocaine, saline, or methylcobalamin and local infiltration of lidocaine or glucocorticoids. For development of PHN including central and peripheral

sensitization,³³ SC mainly acts on peripheral sensitization. Reactivation of *Varicella zoster* virus causes neural damage, inflammation, and tissue edema in the affected tissue. Inflammatory mediators are then released by the injured tissue, which reduces the nociception threshold and activates local nociceptors.³⁴ All these processes promote the development of peripheral sensitization. SC can ameliorate PHN by alleviating local inflammation, blocking peripheral nociceptors, and nourishing injured nerves. In our NMA, after 1 week of treatment, the efficacy of SC was limited, but after 1 month, its efficacy was better than that of PRF. This may be because SC is a long-term treatment that requires frequent injections. The combination of SC and NB was better than either of them alone, or if O3 injection was added, the benefit became significant. However, if PRF, NB, and SC were used together, the efficacy was reduced, and it was worse than that of PRF and PRF + NB. This indicates that too many interventions at the same time is not advisable. Thus, to treat patients with PHN, SC is effective especially when applied with NB and O3 injection. However, all injected medications were combined in this study, so further studies should be performed to explore the difference among various drugs for long periods.

BTX-A is a neurotoxin that is purified from the bacterium *Clostridium botulinum*, and it can inhibit the release of neurotransmitters (including acetylcholine, glutamate, calcitonin gene-related peptide, and substance P) from both motor and sensory neurons.^{35,36} Subcutaneous injection of BTX-A reduces the peripheral nociceptive input, prevents sensitization of nociceptors, and relieves neurogenic inflammation.³⁶ In our study, subcutaneous injection of BTX-A was the most effective measure after 1 week and 1 month of treatment. Furthermore, in the two studies related to BTX-A, subcutaneous injection of BTX-A

showed better pain relief than SC after 2 weeks and 3 months.^{26,27} However, there was no data to compare its long-term effect with other treatments and to evaluate their combined efficacy.

SGB is widely used in pain management, and it changes the function of the sympathetic nervous system. There was only one study that was related to SGB in our analysis. The NMA showed that SGB was worse than NB 1 week after treatment, but its effect was better than NB after 1 month and 2 months. This may be because regulation of sympathetic function is a long-term process and its effect occurs slowly. Thus, to treat patients with PHN, SGB is not a good choice for multiple treatments, and a long course of treatment is required.

PHN treatment must involve interventional therapies at an early stage and include regular anti-neuropathic drug administration. After 1 week of treatment, BTX-A and PRF were the two most effective treatments among all individual interventions. However, if combined therapy was allowed, PRF + NB was the best choice, followed by SC + NB + O3. Too many therapies at the same time was not recommended, because PRF + NB + SC seemed to reduce the efficacy of each treatment, and it was highly invasive for patients. After long-term follow-up, PRF was the most effective therapy to treat patients with PHN.

This study has some limitations. First, only literature published in English was searched for the analysis. Second, participants were patients who had PHN in areas that were innervated by spinal nerves, so this conclusion may not be applicable to PHN in other body areas. Third, many interventions lacked data after the long-term follow-up, making it difficult to compare the patients' long-term efficacy. Finally, because there were no RCTs, many new interventions, such as spinal

cord stimulation and autologous fat grafting were not analyzed in our NMA.³⁷ Therefore, more studies involving these new therapies are needed to develop more effective and safe methods to treat patients with PHN.

Conclusions

Regular anti-neuropathic drug administration that was accompanied by interventional therapies at an early stage is the best choice to treat patients with PHN. BTX-A and PRF are the two most effective individual interventions after 1 week of treatment. However, after long-term follow-up, PRF was the most effective treatment. For combined therapy, PRF + NB was the best choice, followed by SC + NB + O3. Additionally, too many therapies at the same time is not recommended. Clinicians should manage therapeutic regimens in accordance with the patients' specific condition and existing measures to achieve personalized treatment.


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